A one-pot isocyanide-based three-component reaction: synthesis of functionalized keteneimines from 2-hydroxy-benzimidazole

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Reacción de tres componentes a base de isocianuro en un único recipiente: síntesis de cetenaiminas funcionalizadas a partir del 2-hidroxi-bencimidazol

Reacció de tres components a partir del isocianur en un únic recipient: síntesi de cetenaimines funcionalitzades a partir del 2-hidroxi-benzimidazole

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RESUMEN

Se describe una síntesis eficiente de cetenaiminas en un solo recipiente usando un intermedio reactivo 1:1 generado por la adición de isocianuros de alquilo a acetilenodicarboxilato de dialquilo y 2-hidroxibencimidazol.

Palabras clave: Esteres acetilénicos; isocianuros de alquilo; 2-hidroxibencimidazol; cetenaiminas.

SUMMARY

An efficient one-pot synthesis of ketenimines using 1:1 reactive intermediate generated by the addition of alkyl isocyanides to dialkyl acetylenedicarboxylate and 2-hydroxy benzimidazole is described.

Keywords: Acetylenic esters; alkyl isocyanides; 2-hydroxy benzimidazole; ketenimines.

RESUM

Es descriu una síntesi eficient de cetenaimines en un únic recipient fent servir un reactiu intermedi 1:1 produït per l'adició d'isocianurs d'alquil a acetilendicarboxilat de dialquil i 2-hidroxibenzimidazole.

Paraules clau: Èsters acetilènics; isocianurs d'alquil; 2-hidroxibenzimidazole; cetenaimines.

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INTRODUCCIÓN

Benzimidazoles and its derivatives are a class of heterocyclic compounds which are known to play extremely crucial roles in the structures and functions of a number of biologically important molecules. The incorporation of the benzimidazole nuclei is an important synthetic strategy in drug discovery [1]. Applications of several benzimidazole derivatives are include antimicrobial, antihypertensive, anticancer antiulcer, antifungal, antihistamine activity, herbicides, and other veterinary applications as promising drugs in different therapeutic categories [2-9]. The benzimidazole core structure is found in a variety of commercial drugs such as Atacand, Nexium, Micardis, Protonix, and Vermox [10-12]. The benzimidazole moieties express a significant activity against several viruses such as HIV, herpes (HSV-1), RNA influenza, human cytomegalovirus, selective angiotensin II inhibitors, and 5-HT3 antagonists [2-9]. Other applications of benzimidazoles include their use as organic ligands, fluorescent whitening agent dyes and functional materials [13-17]. In addition, benzimidazoles are very important intermediates in synthetic routes [2-9]. Therefore, the construction of these heterocycles has always been of great interest to organic and medicinal chemists and has consequently received much attention [18, 19].

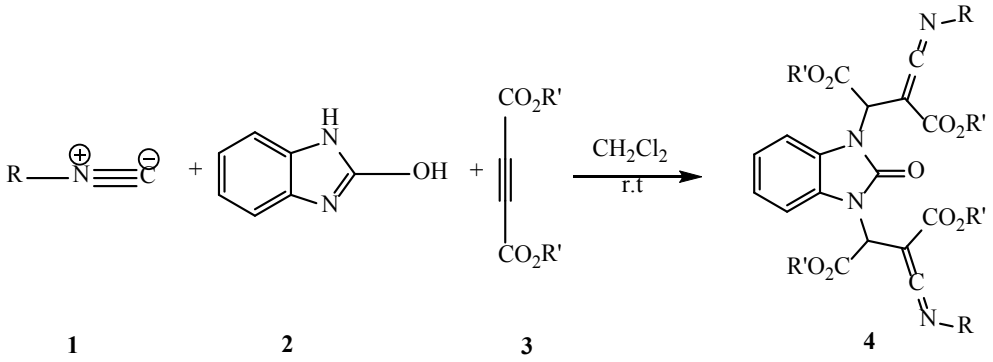
Meanwhile ketenimines have also found widespread use as reactive starting materials for the formation of four-, five-, and six-membered heterocyclic ring systems [20-23]. There has been intense interest in their reactions, such as cycloaddition [24], nucleophilic [25, 26] and electrophilic addition [20].

Recently, we have described a convenient method for preparation of ketenimines, by threecomponent reaction of NH acids, dialkyl acetylene dicarboxylates and alkyl isocyanide [27-29]. In continuation of our interest in the application of isocyanides in MCRs [30, 31], we extend this methodology using 2-hydroxy benzimidazole. Thus, the reaction of alkyl isocyanides 1 and dialkyl acetylene dicarboxylates 3 in the presence of 2-hydroxybenzimidazole 2 leads to functionalized ketenimines 4 (Scheme 1).

MATERIALS AND METHODS

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Perkin Elmer Precisely-100 FTIR spectrometer for KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX300 Avance instrument with $CDCl_3$ as the solvent at 300 and 75 MHz with TMS as internal standard, respectively. The mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Alkyl isocyanides, dialkyl acetylene dicaboxylates and 2-hydroxy benzimidazole were obtained from Fluka and were used without further purification.

Tetramethyl 3,3'-(2-oxo-1*H*-benzo[*d*]imidazole-1,3(2*H*)-diyl)bis(2-((*tert*-butylimino)methylene)succinate) (4a). To a stirred solution of 2-hydroxy benzimidazole (0.26 g, 2 mmol) and tert-butyl isocyanide (0.18 g, 2 mmol) in 10 ml of CH_2Cl_2, dimethyl acetylene dicarboxylate (DMAD) (0.28 g, 2 mmol) was added dropwise and the reaction mixture was then allowed to warm to room temperature and stand



1	R
a	*t*-Bu
b	*Cy*-Hexyl
c	*1,1,3,3-tetra metyl* butyl

3	R'
a	Me
b	Et
c	*t*-Bu

4	R	R'	yeild %
a	*t*-Bu	Me	83
b	*Cy*-Hexyl	Me	76
c	*t*-Bu	Et	86
d	*Cy*-Hexyl	Et	78
e	*Cy*-Hexyl	t-Bu	88
f	*1,1,3,3-tetra metyl* butyl	Me	79
g	*1,1,3,3-tetra metyl* butyl	Et	68

Fig.1 Scheme 1

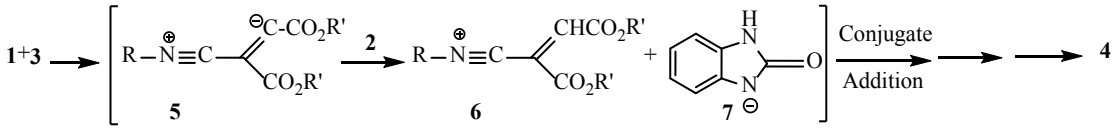


Fig. 2. *Scheme 2*

for 24 h. The solvent was removed under reduced pressure and oil products were purified by preparative TLC on silica gel (Merck silica gel DCFertigplatten 60/Kieselgur F_{254}) 20×20 cm plates using n-hexane-EtOAc (2:1) as eluent. Yield 970 mg (83%), white, powder, mp 151-152 °C. IR spectrum, ν, cm^{-1}: 1667, 1731 (C=O), 2067 (–C=C=N). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.35 (9H, s, 3-CH_3); 1.36 (9H, s, 3-CH_3); 3.68 (6H, s, 2-OCH_3); 3.72 (6H, s, 2-OCH_3); 5.96 (1H, s, CH); 5.98 (1H, s, CH); 7.06-7.08 (2H, m, 2-CH_{Arom}); 7.17-7.21 (2H, m, 2-CH_{Arom}). ^{13}C NMR spectrum, δ, ppm: 29.9 (2-$(CH_3)_3$); 51.7 (2-OCH_3); 52.3 (2-OCH_3); 52.3 (CH);53.0 (CH); 61.1 (-C=C=N); 61.3 (-C=C=N); 62.4 (2-CN); 109.3 (2-CH_{Arom}); 121.6 (2-CH_{Arom}); 128.4 (2-C_{Arom}); 153.1 (C=O); 164.0 (2-CO_2); 168.2 (2-CO_2); 169.8 (2-C=C=N). Mass spectrum (EI, 70 eV), *m/z* (*I*rel, %): 584 $[M]^+$ (14), 486 $[M–C_6H_{12}N]^+$ (19), 380 $[M–C_8H_{16}NO_5]^+$ (57), 358 $[M–C_{11}H_{16}NO_4]^+$ (100). Found, %: C 59.56; H 6.22; N 9.56. $C_{29}H_{36}N_4O_9$. Calculated, %: C 59.58; H 6.21; N 9.58.

Tetramethyl 3,3'-(2-oxo-1*H*-benzo[*d*]imidazole-1,3(2*H*)-diyl)bis(2-((cyclohexylimino)methylene)succinate) (4b). Was prepared similarly to compound **4a** from 2-hydroxy benzimidazole (0.26 g, 2mmol), cyclohexyl isocyanide (0.20 g, 2 mmol) and dimethyl acetylene dicarboxylate (DMAD) (0.28 g, 2 mmol). Yield 966 mg (76%), white, powder, mp 152-154°C. IR spectrum, ν, cm^{-1}: 1670, 1733 (C=O), 2071 (–C=C=N). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.05-2.04 (20H, m, 10-CH_2); 3.68 (6H, s, 2-OCH_3); 3.73 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 3.71 (1H, m, CH); 3.77 (1H, m, CH); 5.96 (1H, s, CH); 5.97 (1H, s, CH); 7.10-7.15 (2H, m, 2-CH_{Arom}); 7.17-7.21 (2H, m, 2-CH_{Arom}). ^{13}C NMR spectrum, δ, ppm: 23.9 (CH_2); 24.1 (CH_2); 24.6 (CH_2); 24.8 (CH_2); 25.4 (CH_2); 25.7 (CH_2); 29.7 (CH_2); 32.1 (CH_2); 32.6 (CH_2); 33.0 (CH_2); 48.9 (2-OCH_3); 51.6 (OCH_3); 52.4 (OCH_3); 52.6 (CH); 52.9 (CH); 59.7 (2-C=C=N); 60.7 (CHN); 60.8 (CHN); 108.7 (CH_{Arom}); 109.1 (CH_{Arom}); 121.6 (CH_{Arom}); 122.0 (CH_{Arom}); 128.5 (C_{Arom}); 129.0 (C_{Arom}); 152.7 (C=O); 163.4 (CO_2); 164.0 (CO_2); 168.0 (CO_2); 168.3 (CO_2); 169.7 (2-C=C=N). Mass spectrum (EI, 70 eV), *m/z* (*I*rel, %): 636 $[M]^+$ (32), 512 $[M–C_8H_{14}N]^+$ (17), 406 $[M–C_{10}H_{18}NO_5]^+$ (39), 384 $[M–C_{13}H_{18}NO_4]^+$ (100). Found, %: C 62.26; H 6.33; N 8.78. $C_{33}H_{40}N_4O_9$. Calculated, %: C 62.25; H 6.33; N 8.80.

Tetraethyl 3,3'-(2-oxo-1*H*-benzo[*d*]imidazole-1,3(2*H*)-diyl) bis(2-((*tert*-butylimino)methylene)succinate) (4c). was prepared similarly to compound **4a** from 2-hydroxy benzimidazole (0.26 g, 2 mmol), tert-butyl isocyanide (0.18 g, 2 mmol) and diethyl acetylene dicarboxylate (DEAD) (0.34 g, 2 mmol). Yield 1.1 g (86%), white, powder, mp 158-59 °C. IR spectrum, ν, cm^{-1}: 1665, 1721 (C=O), 2065 (–C=C=N). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.18-1.25 (12H, m, 4-CH_3); 1.35 (9H, s, 3-CH_3); 1.36 (9H, s, 3-CH_3); 4.05-4.29 (8H, m, 4-OCH_2); 5.95 (1H, s, CH); 5.97 (1H, s, CH); 7.05-7.08 (2H, m, 2-CH_{Arom}); 7.19-7.22 (2H, m, 2-CH_{Arom}). ^{13}C NMR spectrum, δ, ppm: 14.0 (2-CH_3); 14.3 (2-CH_3); 30.0 (2-$(CH_3)_3$); 52.2 (CH); 52.3 (CH); 60.3 (2-C=C=N); 61.7 (OCH_2); 61.8 (OCH_2); 62.0 (2-CN); 62.2 (OCH_2); 62.3 (OCH_2); 109.4 (2-CH_{Arom}); 121.4 (2-CH_{Arom}); 128.4 (C_{Arom}); 128.5 (C_{Arom}); 151.9 (C=O); 167.7 (2-CO_2); 169.2 (2-CO_2); 169.3 (2-C=C=N). Mass spectrum (EI, 70 eV), *m/z* (*I*rel, %): 640 $[M]^+$ (25), 542 $[M–C_6H_{12}N]^+$ (21), 406 $[M–C_{10}H_{20}NO_5]^+$ (54), 386 $[M–C_{13}H_{20}NO_4]^+$ (100). Found, %: C 61.88; H 6.90; N 8.73. $C_{33}H_{44}N_4O_9$. Calculated, %: C 61.86; H 6.92; N 8.74.

Tetraethyl 3,3'-(2-oxo-1*H*-benzo[*d*]imidazole-1,3(2*H*)-diyl) bis(2-((cyclohexylimino)methylene)succinate) (4d). was prepared similarly to compound **4a** from 2-hydroxy benzimidazole (0.26 g, 2 mmol), cyclohexyl isocyanide (0.20 g, 2 mmol) and diethyl acetylene dicarboxylate (DEAD) (0.34 g, 2 mmol). Yield 1.07 g (78%), light-yellow, powder, mp 157-159°C. IR spectrum, ν, cm^{-1}: 1668, 1727 (C=O), 2074 (–C=C=N). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.10-1.84 (20H, m, 10-CH_2); 1.16-1.37 (12H, m, 4-CH_3); 3.41 (^{1}H, m, CH); 3.69 (1H, m, CH); 4.00-4.30 (8H, m, 4-OCH_2); 5.48 (1H, s, CH); 5.56 (1H, s, CH); 7.01-7.23 (4H, m, 4-CH_{Arom}). ^{13}C NMR spectrum, δ, ppm: 13.9 (2-CH_3); 14.0 (2-CH_3); 23.9 (CH_2); 24.6 (CH_2); 24.8 (CH_2); 25.3 (CH_2); 25.4 (CH_2); 25.7 (CH_2); 29.7 (CH_2); 31.9 (CH_2); 32.1(CH_2); 32.6 (CH_2); 48.8 (CH); 49.0 (CH); 54.4 (C=C=N); 54.6 (C=C=N); 61.8 (OCH_2); 61.9 (OCH_2); 62.1 (CHN); 62.1 (CHN); 62.3 (OCH_2); 62.5 (OCH_2); 108.9 (2-CH_{Arom}); 122.0 (CH_{Arom}); 122.2 (CH_{Arom}); 128.9 (2-C_{Arom}); 152.4 (C=O); 163.4 (CO_2); 166.7 (CO_2); 167.4 (CO_2); 167.6 (CO_2); 168.6 (2-C=C=N). Mass spectrum (EI, 70 eV), *m/z* (*I*rel, %): 692 $[M]^+$ (10), 568 $[M–C8H14N]^+$ (11), 432 $[M–C_{12}H_{22}NO_5]^+$ (46), 412 $[M–C_{15}H_{22}NO_4]^+$ (100). Found, %: C 64.17; H 6.97; N 8.08. $C_{37}H_{48}N_4O_9$. Calculated, %: C 64.15; H 6.98; N 8.09.

Tetra-*tert*-butyl 3,3'-(2-oxo-1*H*-benzo[*d*]imidazole-1,3(2*H*)-diyl)bis(2-((cyclohexylimino)methylene)succinate) (4e). was prepared similarly to compound **4a** from 2-hydroxy benzimidazole (0.26 g, 2 mmol), cyclohexyl isocyanide (0.20 g, 2 mmol) and ditert-butyl acetylene dicarboxylate (DTAD) (0.46 g, 2 mmol). Yield 1.41 g (88%), white, powder, mp 169-170 °C. IR spectrum, ν, cm^{-1}: 1662 (C=O), 2070 (–C=C=N). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.11-1.94 (20H, m, 10-CH_2); 1.38 (9H, s, 3-CH_3); 1.40 (9H, s, 3-CH_3); 1.42 (9H, s, 3-CH_3); 1.50 (9H, s, 3-CH_3); 3.42 (1H, m, CH); 3.80 (1H, m, CH); 5.81 (1H, s, CH); 5.86 (1H, s, CH); 7.00-7.06 (2H, m, 2-CH_{Arom}); 7.12-7.18 (2H, m, 2-CH_{Arom}). ^{13}C NMR spectrum, δ, ppm: 23.8 (CH_2); 24.7 (CH_2); 25.3 (CH_2); 25.5 (CH_2); 27.3 (CH_2); 27.4 (CH_2); 27.7 (CH_2); 27.9 (2-$(CH_3)_3$); 28.4 (2-$(CH_3)_3$); 29.7 (CH_2); 32.7 (CH_2); 33.0 (CH_2); 48.4 (CH); 48.6 (CH); 53.0 (2-C=C=N); 60.5 (CHN); 62.1 (CHN); 80.2 (O–C$(CH_3)_3$); 80.3 (O–C$(CH_3)_3$); 82.5 (O–C$(CH_3)_3$); 82.7 (O–C$(CH_3)_3$); 108.7 (CH_{Arom}); 109.3 (CH_{Arom}); 121.4 (2-CH_{Arom}); 121.5 (C_{Arom}); 128.6 (C_{Arom}); 153.3 (C=O); 166.8 (4-CO_2); 168.3 (2-C=C=N). Mass spectrum (EI, 70 eV), *m/z* (*I*rel, %): 804 $[M]^+$ (28), 680 $[M–C_8H_{14}N]^+$ (23), 490 $[M–C_{16}H_{30}NO_5]^+$ (59), 468 $[M–C_{19}H_{30}NO_4]^+$ (100). Found, %: C 67.14; H 8.03; N 6.95. $C_{45}H_{64}N_4O_9$. Calculated, %: C 67.14; H 8.01; N 6.96.

Tetramethyl 3,3'-(2-oxo-1*H*-benzo[*d*]imidazole-1,3(2*H*)-diyl)bis(2 -(((2,4,4-trimethylpentan-2-yl)imino)methylene) succinate) (4f). was prepared similarly to compound **4a** from 2-hydroxy benzimidazole (0.26 g, 2 mmol), 1,1,3,3-tetramethyl-butyl isocyanide (0.28 g, 2 mmol) and dimethyl acetylene dicarboxylate (DMAD) (0.28 g, 2 mmol). Yield 1.1 g (79%), white, powder, mp 160-162°C. IR spectrum, ν, cm^{-1}: 1652 (C=O), 2073 (–C=C=N). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.01 (18H, s, 6-CH_3); 1.40 (6H, s, 2-CH_3); 1.42 (6H, s, 2-CH_3); 1.57 (2H, s, CH_2); 1.59 (2H, s, CH_2); 3.65 (6H, s, 2-OCH_3); 3.72 (6H, s, 2-OCH_3); 5.96 (1H, s, CH); 5.99 (1H, s, CH); 7.05-7.08 (2H, m, 2-CH_{Arom}); 7.18-7.23 (2H, m, 2-CH_{Arom}). ^{13}C NMR spectrum, δ, ppm: 30.7 (CH_3); 30.8 (CH_3); 30.9 (CH_3); 31.0 (2-$(CH_3)_3$); 31.4 (CH_3); 31.6 (2-C); 51.4 (2-CH_2); 52.2 (OCH_3); 52.3 (OCH_3); 52.9 (2-OCH_3); 54.4 (2-CH); 60.5 (C=C=N); 60.6 (C=C=N); 65.1 (C-N); 65.2 (C-N); 109.4(CH_{Arom}); 109.5 (CH_{Arom}); 121.5 (2-CH_{Arom}); 128.3 (C_{Arom}); 128.4 (C_{Arom}); 152.1 (C=O); 162.1 (2-CO_2); 168.3 (2-CO_2); 170.0 (2-C=C=N). Mass spectrum (EI, 70 eV), *m/z* (*I*rel, %): 696 $[M]^+$ (12), 542 $[M–C_{10}H_{20}N]^+$ (15), 432 $[M–C_{12}H_{24}NO_5]^+$ (38), 414 $[M–C_{15}H_{24}NO_4]^+$ (100). Found, %: C 63.80; H 7.51; N 8.04. $C_{37}H_{52}N_4O_9$. Calculated, %: C 63.77; H 7.52; N 8.04.

Tetraethyl 3,3'-(2-oxo-1*H*-benzo[*d*]imidazole-1,3(2*H*)-diyl) bis(2-(((2,4,4-trimethylpentan-2-yl)imino)methylene)succinate) (4g). was prepared similarly to compound **4a** from 2-hydroxy benzimidazole (0.26 g, 2 mmol), 1,1,3,3-tetramethyl-butyl isocyanide (0.28 g, 2 mmol) and diethyl acetylene

dicarboxylate (DEAD) (0.34 g, 2 mmol). Yield 1.02 g (68%), white, powder, mp 164-166°C. IR spectrum, ν, cm^{-1}: 1654 (C=O), 2074 (–C=C=N). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.01 (9H, s, $(CH3)_3$); 1.03 (9H, s, $(CH3)_3$); 1.09-1.46 (12H, m, 4CH3); 1.41 (6H, s, 2-CH3); 1.48 (6H, s, 2-CH3); 1.58 (2H, s, CH2); 1.67 (2H, s, CH2); 4.08-4.53 (8H, m,4-OCH_2); 5.95 (1H, s, CH); 5.98 (1H, s, CH);7.05-7.23 (4H, m, 4-CH_{Arom}). ^{13}C NMR spectrum, δ, ppm: 14.0 (2-CH_3); 14.4 (2-CH_3); 30.7 (CH_3); 30.9 (CH_3); 31.1 (2-$(CH_3)_3$); 31.4 (CH_3); 31.6 (C); 31.7 (C); 32.0 (CH_3); 52.4 (2-CH_2); 54.4 (CH); 58.5 (CH); 59.6 (2-C=C=N); 60.2 (2-OCH_2); 62.0 (2-OCH_2); 65.0 (C-N); 65.1 (C-N); 109.4(CH_{Arom}); 109.5 (CH_{Arom}); 121.3 (2-CH_{Arom}); 128.0 (C_{Arom}); 128.5 (C_{Arom}); 152.5 (C=O); 162.9 (CO_2); 163.1 (CO_2); 167.8 (2-CO_2); 169.5 (C=C=N) ; 169.6 (C=C=N). Mass spectrum (EI, 70 eV), *m/z* (*I*rel, %): 752 $[M]^+$ (24), 600 $[M - C_{10}H_{20}N]^+$ (28), 462 $[M–C_{14}H_{28}NO_5]^+$ (53), 442 $[M–C_{17}H_{28}NO_4]^+$ (100). Found, % C 65.42; H 8.02; N 7.40. $C_{41}H_{60}N_4O_9$. Calculated, %: C 65.40; H 8.03; N 7.44.

RESULTS AND DISCUSSION

The reaction proceeded spontaneously at room temperature in dichloromethane, and was completed within a few hours. The structure of **4** was determined on the basis of its elemental analyses, mass spectrum (MS), 1H and 13C NMR and IR spectroscopic data.

The 1H NMR spectrum of 4a exhibited six signals for tert-butyl (δ = 1.35 and 1.36 ppm), metoxy (δ = 3.68 and 3.72 ppm), and methine (5.96 and 5.98 ppm) protons. The aromatic moiety appeared as a multiplet at 7.06–7.08 and 7.17–7.21 ppm. The ^{13}C NMR spectrum of compound **4a** showed distinct 15 resonances in agreement with the proposed structure. Partial assignments of these resonances are given in the Experimental. The ^1H NMR spectra of compounds **4b–4g** are similar to that of compound **4a**, except for the signals of the alkyl isocyanides and ester moiety. The structural assignments of compounds **4a–4g** made on the basis of their NMR spectra were supported by their IR spectra. Of special interest is the strong ketenimine absorption band at about 2067 cm^{-1}.

It is conceivable that the reaction involves the initial formation of the 1:1 zwitterionic intermediate **5** between the isocyanide and dialkyl acetylenedicarboxylates. The protonation of compound **5** by the NH-acidic **2** leads to intermediate **6**. Subsequent attack of the resulting nucleophile **7** on the positively charged ion **6** ketenimines. The same path for another NH was occurred, to product ketenimines **4**. Similar mechanistic scheme can be considered for formation of compounds **4a–4g** (Scheme 2).

CONCLUSION

In conclusion, we have found a simple and efficient method for the preparation of highly functionalized ketenimines. The present method carries the advantage that not only the reaction is performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

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